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APPLICANT(S)	: BOWEN, Philip J. et al
SERIAL NO.	: 10/502,080
FILED	: October 8, 2004
FOR	: ~~SOLENSOPSIN~~ A, B AND ANALOGS AS NOVEL ANGIOGENESIS INHIBITORS Solenopsin
GROUP ART UNIT	: 1612
Examiner	: Brian M. Gulledge

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF DR. JACK L. ARBISER

I, Jack L. Arbiser declare as follows:

1. I am a co-inventor of the subject matter of the above-referenced patent application.

2. I am a citizen of the United States of America.

3. In 1983, I received a B.S. degree in Chemistry from Emory University, Atlanta, Georgia.

4. In 1991, I received a Ph.D. degree in Genetics and a MD degree in Medicine from Harvard Medical School, Boston, Massachusetts.

5. From 1994-1998, I participated in the Howard Hughes Postdoctoral Fellowship, Laboratory of Judah Folkman, M.D., Harvard Medical School, Boston Massachusetts.

6. Since 1991, I have studied the mechanisms of how oncogenes and tumor suppressor genes regulate angiogenesis and tumorigenesis. This work has resulted in the

16. From 1991 to 1992, I was an Intern in Internal Medicine, Beth Israel Hospital, Boston, Massachusetts.

17. From 1985 to 1991, I was in the Medical Scientist Training Program, Department of Genetics, Harvard Medical School, Boston, Massachusetts.

18. In 1984, I was a Research Assistant, Department of Rheumatology, Massachusetts General Hospital, Boston, Massachusetts.

19. In 1983, I was a Research Assistant, Department of Pediatrics, Emory University, Atlanta, Georgia.

20. In 1979, I was an Undergraduate Research Assistant, Department of Chemistry, Emory University, Atlanta, Georgia.

21. I have received numerous awards and honors for my scientific work including receiving the Albert E. Levy Scientific Research Award for Senior Investigator in 2007, and receiving the Emory School of Medicine Dean's Clinical Scholar award from 2000-2003 and 2004-2006 among other awards and honors.

22. I am a member of the Emory Medical Student Research Committee (2001- 2008 present) and the VA Research and Development Committee (2007-present). I am also a member of the Dermatology Foundation Metical and Scientific Committee External Advisory Board, University of Arizona Cancer Center, the Sturge-Weber Foundation Scientific Advisory Board (2001-present) and the American Academy of Dermatology-NAID Liaison (1998-~~present~~ 2005). I was an Organizer for the 48th Montagna Annual Symposium on the Biology of Skin, Snowmass Colorado (1999). I have been a Membership Chair of the Society for Investigative Dermatology (2001-2002) and a Resident/Fellow Representative for the Society of Investigative Dermatology

(1995-1997).

23. I have been a member of the following societies: the American Association for Cancer Research, The Society for Investigative Dermatology, the American Academy of Dermatology, the Tuberous Sclerosis Alliance, the Dermatology Foundation and the Sturge-Weber Foundation.

24. I am on the Editorial Boards for Pigment Cell Research (2007-2009) and Journal of Investigative Dermatology (2001-present). I have been on the Editorial Boards for Journal of the Cutaneous Medicine and Surgery (2002-2005) and Journal of the American Academy of Dermatology (2001-2004). I was also a Guest Editor for Seminars in Cancer Biology, Karolinska Institute.

25. I have published over 150 scientific papers and I have published extensively in the scientific area of cancer research, including the mechanism by which cancer occurs, including the role of angiogenesis in cancer pathogenesis, including tumorigenesis.

26. I am familiar with United States patent application serial number 10/502,080, of which I am a co-inventor. I understand that the presently pending claims are directed to a method of treating cancer or a tumor in a patient comprising administering to a patient in need an effective amount of a composition which comprises a compound as otherwise set forth in the presently pending claims, namely claims 40, 50-56 and 66. Essentially, the presently pending claims are directed to the discover that compositions which contain effective amounts of a compound as otherwise set forth in the presently pending claims are effective to treat a number of cancers and tumors. This is based upon the fact that the compounds which are set forth in presently pending claims 40, 50-56 and 66 inhibit cancer and/or tumor growth by a mechanism which inhibits angiogenesis in the cancer/tumor tissue. By inhibiting angiogenesis, the presently claimed methods provide a generic approach to the treatment of any number of cancers and tumors as set forth in presently pending claims 40, 50-56 and 66.

27. It is my opinion that the presently claimed methods of treating tumors and/or cancer are useful and are expected to work as described, given that angiogenesis is an important mechanism by way tumors and/or cancer grow and elaborate and the presently claimed methods set forth in pending claims 40, 50-56 and 66 are directed to methods which utilize the inhibition of angiogenesis as a general mechanism to treat tumor and/or cancer.

28. Angiogenesis comprises the development of a new vasculature for a tissue with increased metabolic demand. In adult life, the new tissue is likely to be a tumor or cancer, either benign or malignant, or an inflammatory process, such as psoriasis, inflammatory bowel disease, arthritis, asthma, multiple sclerosis, type II diabetes, lupus, and other diseases. The major sources of the blood vessel cells (endothelial cells) that are required for this process are recruitment of blood vessel cells from local pre-existing capillaries, or recruitment of cells from bone marrow that can turn into endothelial cells. Both processes contribute to the vascularization of a tumor or an inflammatory process. One of the commonalities of both inflammatory and tumor derived (neoplastic processes) is that they elaborate factors that recruit endothelial cells. The major factors for these processes include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), inflammatory cytokines (such as interleukin-8, and other factors), which stimulate the migration and proliferation of endothelial cells. The laboratory of Judah Folkman, MD, proved the absolute requirement of angiogenesis for the growth of malignant tumors, obesity, maintenance of pregnancy, and development of atherosclerotic plaques. Based upon this pioneering work, angiogenesis inhibitors have been developed for the treatment of human diseases, in particular the treatment of tumors and cancer.

29. Two strategies have been developed for the assessment of angiogenesis inhibitors. The first is direct inhibition, in which the activity of growth factors on the receptors is directly antagonized. The second is indirect inhibition, in which the ability of tumors to produce growth factors is inhibited. The phosphoinositol-3 kinase pathway, which is activated in virtually all tumors, is implicated in both direct and indirect angiogenesis inhibition.

30. Direct antiangiogenesis inhibition is now in clinical use for the treatment of cancer. The most prominent example is that of avastin (bevacizumab) that directly blocks the activity of VEGF on endothelial cells. Avastin is commonly used for the treatment of kidney and colon cancer, and more recently in brain cancer (glioblastoma). While avastin has been shown to be of clinical benefit, it is not curative and has well known side effects, such as hypertension and bleeding. In addition, the tumor hypoxia that is induced by avastin is thought to cause adaptation in the tumor, such as increased local invasion and elaboration of more growth factors in order to relieve the avastin-induced tumor hypoxia. Other strategies are being developed, but it is likely that any strategy that increased tumor hypoxia by itself will ultimately not cure a tumor.

31. Indirect inhibition of angiogenesis is an attractive strategy that has not been sufficiently explored. My studies in the Folkman lab, published in the Proceedings of the National Academy, were the first to demonstrate that blockade of phosphoinositol-3 kinase was able to inhibit the growth of a tumor *in vivo*. Blockade of phosphoinositol-3 kinase is an attractive strategy for several reasons. First, it blocks the production of growth factors by the tumor. Second, it causes increased apoptosis (programmed cell death) in tumors themselves. Finally, it is believed to prevent the metabolic adaptations in tumors caused by antiangiogenic therapies. Since phosphoinositol-3 kinase is such an important target, we regard it as a major focus to inhibit this pathway and to treat tumors and cancer. We discovered that solenopsin, a naturally occurring alkaloid in the venom of the fire ant (Solenopsis invicta), is a potent inhibitor of this enzyme. In addition, we have shown that this compound claimed in the present invention is a potent inhibitor of angiogenesis in the zebrafish model. See the attached references, Arbiser, et al, *Blood*, 15 January 2007, Volume 109, Number 2, pages 560-565 and Park, et al., *Journal of Infectious Diseases*, 15 October 2008, 198, 1198-201. The inhibitory activity, small molecular size and stability of solenopsin, which make it amenable to topical, systemic and oral administration, make it an attractive molecule for the treatment of tumors and cancer. It thus represents close to an ideal compound for providing generic therapy against a variety of cancerous tissue.

32. Given the exceptional inhibitory activity solenopsin displays against phosphoinositol-3 kinase and the direct and indirect role that phosphoinositol-3 kinase plays in promoting angiogenesis, a critically important process in tumor/cancer growth and elaboration, it is my expectation that solenopsin will prove to be an effective agent against tumors and cancer by inhibiting angiogenesis in cancer tissue through phosphoinositol-3 kinase. By virtue of the inhibitory activity of the compounds which are presently claimed in the pending claims which are directed to a method of treating tumors and cancer, it is my expectation that these compounds will prove to be effective anti-cancer agents against a broad range of tumors and cancer.

33. I further declare that all statements made herein of my own personal knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10/4/10

Jack L. Abiser, MD, PhD